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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/973,576	04/02/98	MALFROY-CAMINE	B	15390-00013U

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EXAMINER	
SCHWADRON, R	
ART UNIT	**PAPER NUMBER**
1644	10

DATE MAILED: 07/15/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/973,576	Malfroy-Camine
Examiner	**Group Art Unit**
Ron Schwadron, Ph.D.	1644

☒ Responsive to communication(s) filed on *5/3/99 and 5/28/99* .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-22* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-22* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. Claims 1-22 are under consideration. Claim 23 has been cancelled. Claims 1,9,14,19,20,22 have been amended.

RESPONSE TO APPLICANTS ARGUMENTS

2. The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and © may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 14-23 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1,2,4-12,24,29-33 of copending application Serial No. 08/483,944. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reasons. While the two sets of claims differ in scope, both sets of claims encompass methods which make the same products and compositions which contain the same ingredients. Therefore, the two sets of claims under consideration in this rejection would have been prima facie obvious in view of each other to one of ordinary skill in the art at the time the invention was made for the aforementioned reasons.

Applicant has indicated in the instant amendment that this issue will be addressed at a later date.

4. Applicant needs to update the status of all US Patent applications (eg. abandoned, etc.) disclosed in the specification (eg. page 1 and page 3).

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

There is no support in the specification as originally filed for the recitation of "organ uptake" in claims 1,9,14,19,20,22. Regarding applicants comments about the specification and support for the claimed invention, the specification discloses that the claimed invention has "enhanced organ uptake" (eg. see page 1, lines 10-13) or "increased capacity to cross vascular barriers and access parenchymal cells of various organs" (see page 5, lines 26-30). The proposed claims do not recite "enhanced organ uptake" and thus encompass lipidized proteins that do not have enhanced organ uptake compared to unlipidized protein used in said lipid/protein conjugate. There is no disclosure in the specification as originally filed of such lipidized proteins (do not show enhanced organ uptake). Therefore, the scope of the written description in the specification as originally filed is not commensurate with the scope of the proposed claimed (eg. the proposed claims constitute new matter).

7. Claims 9-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession

of the claimed invention.

There is no support in the specification as originally filed for the recitation of "or" in claims 9,14,19 and 20. The recitation of "or" indicates that the claimed antibody can have any of one of the three properties recited in said claim (eg. transvascular transport or organ uptake or intracellular localization). However, lipidized antibodies with only one of the aforementioned characteristics (eg. organ uptake, but not intracellular localization) in the absence of the other functional properties are not disclosed in the specification as originally filed. Regarding applicants comments about various passages of the specification, said passages do not disclose lipidized antibodies which possess one of the functional attributes recited in the claim in the absence of the other functional properties recited in the claim(eg. organ uptake, but not intracellular localization).

8. Claim 19 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 is indefinite in the recitation of "antibdody". A preferred substitution is "antibody".

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-22 stand rejected under 35 U.S.C. § 103 as being unpatentable over Kabanov et al. (pages 33-36) or Kabanov et al. (pages 63-67) in view of Bischofberger et al. and Rodwell et al. for the reasons elaborated in the previous Office Actions. Applicants arguments have been considered and deemed not persuasive.

The claims are drawn to lipidized proteins comprising a polypeptide covalently linked to a lipid through a carbohydrate moiety, a method for making said conjugates, compositions containing said lipidized proteins and a method of diagnosis using said proteins. Kabanov et al.

teach lipidized proteins (including antibodies) and methods for making said proteins (see entire document, either reference). Kabanov et al. do not teach that the lipidized proteins comprise a polypeptide covalently linked to a lipid through a carbohydrate moiety. Bischofberger et al. teach that an aminolipid (lipoamine) can be used for attaching a lipid to an immunoconjugate (page 13, paragraph three). A routineer would have realized that said method could have also been used to attach said lipid to an oxidized antibody saccharide, because Rodwell et al. teach that amine containing compounds (e.g. lipoamine) can be attached to antibodies by oxidation of antibody saccharides to aldehydes which can react with amine containing compounds (page 2635, first column, second sentence, *Discussion* section). Bischofberger et al. teaches a wide variety of lipids can be used in the invention (page 4, third paragraph), and coupled with his previous teaching of a lipoamine for lipid conjugates, a routineer would have derived the lipoamine compounds of claims 4-6. A routineer would have applied the instant method to any glycoprotein. The antibodies taught by Kabanov et al. consist of mu or gamma heavy chains and is coded for by an immunoglobulin superfamily gene. A routineer would have used the instant method to lipidize monoclonal antibodies. A routineer would have used the instant method to produce lipidized proteins or antibodies. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed inventions because Kabanov et al. teach lipidized proteins (including antibodies) and methods for making said proteins, Bischofberger et al. teach that an aminolipid (lipoamine) can be used for attaching a lipid to an immunoconjugate and a routineer would have realized that said method could have also been used to attach said lipid to an oxidized antibody saccharide, because Rodwell et al. teach that amine containing compounds (e.g. lipoamine) can be attached to antibodies by oxidation of antibody saccharides to aldehydes which can react with amine containing compounds. A routineer would have lipidized antibodies which bind intracellular proteins because the major purpose of the invention is to deliver proteins intracellularly. One of ordinary skill in the art would have been motivated to do the aforementioned because Kabanov et al. teaches lipidized antibodies and Rodwell et al. teaches the advantages of preparing antibody conjugates via oligosaccharide linkage (see abstract). Kabanov et al. teach that lipidized antibodies can be used to target intracellular proteins (see pages 65-67). A routineer would have administered said lipidized antibody in vivo in a pharmaceutical composition. Kabanov et al. teach lipidized antibody against viral protein (see page 65). A routineer would have prepared lipidized antibody against any art known viral protein.

Based on the teachings of Kabanov et al., it would have been obvious to a routineer that lipidized antibodies could have been used in any art known assay (eg. immunoassay) that conventional antibodies were used, wherein it was desirable to detect intracellular antigens (eg. viral antigens). Labeled antibodies for use in immunoassays are well known in the art.

Regarding applicants comments about a declaration from Malfroy-Camine filed with the amendment filed 5/3/99, no such declaration has been received in the instant application. Regarding applicants comments that the lipidized antibodies taught by Kabanov et al. have reduced affinity for antigen, there is no evidence of record to support such an allegation. Regarding applicants comments that the antibodies taught by Kabanov et al. are "covalent liposomes", the lipidized antibodies taught by Kabanov et al. contain lipid chemically conjugated to an antibody. Said antibodies are not liposomes and would not be encompassed by the term liposome any more than would the antibodies recited in the claims, because both lipidized antibodies are antibodies chemically conjugated to lipid. The antibodies taught by Kabanov et al. are not identical to the claimed antibodies. However, the current rejection does not state that they are identical. Regarding applicants comments about Horan et al., Horan et al. teaches that using appropriate lipids and screening methods that it is possible to produce a lipidized molecule which is retained in the cell membrane. However, to produce such a molecule it is necessary to screen for lipidized molecules which contain a particular lipid which allows membrane localization (eg. see Horan et al., claim 1). In fact, the invention of Horan et al. recites numerous structural limitations upon the lipid used in the construct wherein said lipid permits surface membrane retention (see claim 1). Horan et al. does not teach that lipidized antibodies will not localized intracellularly. Horan et al. teaches that certain types of lipidized antibodies can be produced which localize in the cell membrane, if screening is performed to select antibodies with such a property. The art already recognized that lipidized antibodies which bound an intracellular antigen could be produced (see Kabanov et al.). Kabanov et al. teach that lipidized antibodies can be produced which intracellularly localize in cells. The Horan et al. teaching does not negate the teaching of Kabanov et al. that lipidized antibodies which localize intracellularly can be produced because Horan et al. teach that by appropriate screening techniques that it is possible to select a lipid for use in a lipid/molecule conjugate wherein said conjugate localizes in the surface membrane if the lipid used exhibits the property of localizing in the cell surface membrane. Kabanov et al. disclose that lipidized antibodies can be produced which localize intracellularly when a lipid which has that property is conjugated to an antibody which binds such an intracellular. The teachings of Kabanov

et al. and Horan et al. indicate that upon use of the appropriate lipid/antibody combination that is possible to produce a lipidized antibody which localizes to the cell membrane or localizes intracellularly.

The Kabanov et al. references teach lipidized antibodies (see entire document) and that said lipidized antibodies can "translocate across lipid membranes and penetrate intact cells" (see Kabanov et al., abstract). Thus, the art recognized that lipidized antibodies could be made and that lipidized antibodies can "translocate across lipid membranes and penetrate intact cells". The Kabanov et al. references teach lipidized antibodies (see entire document) and that said lipidized antibodies can "translocate across lipid membranes and penetrate intact cells" (see Kabanov et al., abstract). These lipidized antibodies are functionally equivalent to the claimed antibodies, differing only in the site of conjugation of the lipid moiety. Thus, Kabanov et al. have already established that lipidized antibodies can be made. Kabanov et al. teach that the lipidized antibodies produced by their method are functionally active (eg. see page 34, last paragraph, column 1). Kabanov et al. also teach the lipidization of other biomolecules, including toxins (page 33, second column, last paragraph), oligonucleotides (see Figure 2) and proteins (see page 35, first column, last paragraph). Thus Kabanov establishes that a variety of different biomolecules can be lipidized. Rodwell et al. teach that "oligosaccharide modification is a preferred method of preparing antibody conjugates" (see page 2632, Abstract, last sentence). This statement provides the motivation to produce lipidized antibodies using oligosaccharide modification. Rodwell et al. also teach that while oligosaccharide modification is a preferred method of preparing antibody conjugates, that the art recognizes that antibody conjugates can be formed using a variety of different techniques and that said conjugates are functionally active. In view of this teaching, it would have been obvious that lipidized antibodies conjugated using the technique taught by Rodwell et al. would have comparable activity to those taught by Kabanov et al. Furthermore, Rodwell et al. teach methods for preparing oligosaccharide modified antibody conjugates (see entire document). Regarding applicants comments about reasonable expectation of success, Rodwell et al. have established that antibodies can be conjugated to other molecules via oxidized oligosaccharide molecules and Kabanov et al. teach lipidized antibodies which are functionally active. Kabanov et al. teach lipidized antibodies which are functionally active, while Rodwell et al. teach methods for preparing oligosaccharide modified antibody conjugates. With regards to applicants comments about the motivation to combine references, Rodwell et al. teach that "oligosaccharide modification is a preferred method of preparing antibody conjugates" (see

page 2632, Abstract, last sentence). All of the components used in the method of the instant invention are disclosed in the cited prior art. With regards to applicants comments about reasonable expectation of success, Rodwell teaches that antibodies can be conjugated to amine containing reagents via oxidized oligosaccharides (see Abstract). This is the same chemical reaction used to create the lipidized protein of the instant invention. Regarding applicants comments about the functional properties of the lipidized antibodies taught by Kabanov et al., there is no evidence of record that the lipidized antibodies of Kabanov et al. have any functional property different from that of the claimed invention.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

12. Claims 14,15,19,20 remain rejected under 35 U.S.C. 102(e) as being anticipated by Horan et al. (US Patent 5,665,328) for the reasons elaborated in the previous Office Action. Applicants arguments have been considered and deemed not persuasive.

Horan et al. teach lipidized glycoproteins including antibodies wherein the carbohydrate side chain of the glycoprotein is oxidized and a lipophilic amine is reacted to form a lipidized protein (see column 14, lines 39-46) and column 5, second paragraph. Horan et al. teach that said lipidized proteins can contain a radionucleotide (see column 7, second paragraph). Horan et al. teach compositions containing lipidized protein and a pharmaceutically acceptable carrier. Horan et al. teach that the lipidized protein is made as per the methods of claim 1-3 (see column 14, lines 39-46). Antibodies are naturally occurring glycoproteins that are members of the immunoglobulin superfamily. Horan et al. teach the use of monoclonal antibodies in the claimed invention (see column 5, second paragraph). It is an inherent property of said antibodies that said antibodies are capable of "organ uptake" because said antibodies bind cells and all cells are part of some organ.

Regarding applicants comments, the claimed inventions recite that the antibody is capable of "transvascular transport, organ uptake or intracellular localization". The lipidized antibodies taught by Horan et al. are capable of "organ uptake" because said antibodies bind cells and all cells are part of one "organ" or another. For example, white blood cells are part of blood or bone marrow. Horan et al. teach lipidized antibodies which bind white blood cells(see column 3 and column 6). The claimed inventions do not state that the antibodies are restricted to those that are capable of intracellular localization. The instant rejection has been withdrawn as it previously applied to claims 1-3,7,8 because said claims are now limited to antibodies that are capable of "transvascular transport, organ uptake and intracellular localization". Regarding applicants comments about the telephonic interview, while there was agreement that the rejection would be withdrawn in view of amended claims which recited that the antibodies were capable of "transvascular transport, organ uptake and intracellular localization", there was no discussion or agreement with regards to claims that recited language "transvascular transport, organ uptake or intracellular localization".

13. No claim is allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official

Gazette, 1096 OG 30 (November 15, 1989). Papers should be faxed to Group 1600 at (703) 305-3014.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Ron Schwadron whose telephone number is (703) 308-4680. The examiner can normally be reached Monday through Thursday from 7:30 to 6:00. A message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

RONALD B. SCHWADRON
PRIMARY EXAMINER
GROUP ~~1800~~ 1600

Ron Schwadron, Ph.D.
Primary Examiner
Art Unit 1644
July 14, 1999